



## Review article

## A review of Agent Orange and its associated oncologic risk of genitourinary cancers

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**Abstract**

Agent Orange is an herbicide sprayed widely in Vietnam that is linked to a variety of malignancies in as early as 1991. Since then, there has been concern for, and subsequent interest in studying, the potential connection between Agent Orange and other malignancies. In the past 2 decades, there have been significant changes in the opinion of the National Academy of Science regarding Agent Orange and certain genitourinary malignancies. Herein, we review the literature regarding the potential link between Agent Orange and various urological cancers, including prostate, bladder, testicular, and renal cancers. © 2017 Elsevier Inc. All rights reserved.

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**1. Background**

Agent Orange is an herbicide sprayed widely in Vietnam from August 1965 to February 1971, and contains 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). TCDD has been shown to cause direct DNA damage and has been linked to a variety of malignancies, especially non-Hodgkin's lymphomas, soft-tissue sarcomas, and cutaneous T-cell lymphomas [1,2]. With these discoveries, there was significant concern that Agent Orange could increase the risk of other cancers as well. In recent years, there has been interest in studying the potential connection between Agent Orange and urologic malignancies. In 1991, Congress enacted the Agent Orange Act, which mandated the National Academy of Science to periodically review the available literature regarding herbicidal exposure and various disease states. In the past 2 decades there have been significant changes in the Academy's expert opinions regarding Agent Orange and certain genitourinary malignancies. In 1998, the National Academy of Science stated that there was "limited or suggestive evidence" of an

increased association between Agent Orange and prostate cancer [3]. A recent update in March 2016 by the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides has suggested that there is "limited or suggestive evidence" of an increased association between Agent Orange and bladder cancer [4]. Herein, we review the literature and case-control studies regarding the potential link between Agent Orange and various urological cancers, including prostate, bladder, testicular, and renal cancers. Our paper serves to raise the question that perhaps specific guidelines are needed to address screening and possible changes in surveillance protocols among patients who have had toxic chemical exposures.

**2. Biological plausibility of Agent Orange and malignancy**

Several studies have provided significant evidence corroborating TCDDs association with malignancy. TCDD is easily and rapidly absorbed via alimentary tract, yet eliminated slowly. Oral administration can lead to 50% to 93% absorption of the administered dose [5]. The half-life is exceedingly long, with some studies demonstrating a

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half-life of up to 7.2 years [6]. The mechanism by which TCDD promotes carcinogenesis has not been completely elucidated, but it is known that TCDD interacts intracellularly with the ligand-activated aryl hydrocarbon receptor (AHR) or the aryl hydrocarbon receptor nuclear translocator (AHNR), or both [7]. This transcription factor alters gene expression of factors such as platelet-derived growth factor and vascular endothelial growth factor, which are heavily implicated in carcinogenesis [7]. TCDD may also indirectly promote aberrant cell growth by binding to a portion of the AHR/AHNR complex, which would also alter gene expression and cell function that potentially promotes carcinogenesis [7]. These are mechanisms by which chemical compounds such as TCDD provide intracellular signals that can affect the nuclei of cells and lead to increased risk of malignancy.

### 3. Prostate cancer

Prostate cancer has been the most common noncutaneous malignancy in the United States since 1984, now accounting for 27% of all cancers and it is estimated that 1 in 7 men alive today will be diagnosed with prostate cancer [8]. The first study demonstrating an associated increased risk of prostate cancer due to Agent Orange exposure was a case-control study in 2004 at the Michigan Veterans Affairs hospital, which showed that men with prostate cancer were approximately 2 times more likely to report previous exposure to Agent Orange (odds ratio = 2.06, 95% CI: 0.81–5.23) [9]. In 2013, the first statistically significant study describing Agent Orange as a risk factor for high-grade prostate cancer was completed at the Portland, Oregon Veterans Affairs hospital. This study described not only the positive association between herbicide exposure and the overall risk of prostate cancer, but also a twofold increased risk for high-grade (Gleason score: 8–10) prostate cancer [10]. Additional studies concluded that prostate cancer was diagnosed at a younger age and was of a more aggressive variant in exposed veterans [11]. Other international studies such as the Agent Orange Exposure and Prevalence of Self-reported Diseases based out of Korea further demonstrated the same relationship as was seen in the US population studies [12]. Although based on self-reported survey data, the Korean study with more than 100,000 respondents did demonstrate a greater than twofold risk of prostate cancer in the high exposure group as compared to the control group. Statistically significant and associated studies describing incidence (Table 1) and mortality (Table 2) are detailed later.

As seen in the aforementioned tables, several studies have revealed a statistically significant increased incidence of prostate cancer in veterans exposed to Agent Orange [10,13–18]. The Akhtar et al. [15] study was first to investigate cancer incidence among United States Vietnam War veterans. Overall, there is an increased incidence of

prostate cancer in those who served longer in Vietnam and had higher serum levels of TCDD [13,14]. However, no study has been able to demonstrate increased risk of mortality among those exposed to Agent Orange [19,20]. A review of the cited studies also reveals that although there are many statistically significant studies, most studies utilize small sample sizes with the exception of 2: The Northern California self-reported survey-based study of 239 exposed patients with prostate cancer, and the Australian-based population study of 692 exposed patients with prostate cancer [17,18]. In the former study, Chamie et al. [17] provided one of the more comprehensive studies which found that compared to unexposed men, Agent Orange-exposed men were diagnosed with prostate cancer at a younger age, had a twofold increase in the proportion of Gleason scores 8 through 10 cancer, and were more likely to have metastatic disease at presentation. The Australian cohort study was a major contributor to the 2006 Agent Orange update from the National Academy of Sciences, where the stance was elevated to “limited or suggestive evidence” of an increased association between Agent Orange and prostate cancer, and that stance remains to this day [4,18]. Veterans who served in Vietnam are around the same age as the average age of diagnosis of prostate cancer, age 67 [21], warranting increased need of prostate cancer screening in veterans, specifically in those veterans who were subject to environmental exposures.

### 4. Bladder cancer

Bladder cancer is a “cancer of the environment and age” [22]. Links confirming genetic susceptibility to bladder cancer have been made, such as *NAT2* slow acetylator and *GSTM1*-null genotypes [23]; however, external risk factors appear to be of primary importance. The earliest chemical agents associated with bladder cancer were Benzidine and  $\beta$ -naphthylamine in dye and rubber workers [24]. However, the most important known risk factor for bladder cancer is tobacco smoke inhalation. Over the past several decades, there has been considerable debate regarding the carcinogenic effect of Agent Orange on the urothelium, specifically in the bladder. The debate remains contentious, as bladder cancer has not yet been considered a service-connected disease process for Vietnam Veterans.

In their tenth biennial report, the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides changed their previous stance on bladder cancer, reporting that “epidemiologic results concerning an association between exposure to the chemicals of interest (COIs) and bladder cancer had accrued to now constitute limited or suggestive evidence of an association” [4]. This change provides a significant shift in previous reports which stated that there was “inadequate or insufficient information to determine whether there [was] an association” [22].

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